## Supplemental material 1: Data management plan

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# Attachments

# 1 PLAN OBJECTIVE.

The Data Management Plan (DMP) describes all the data management procedures that take part during the clinical trial. The timing and the tasks that occur in each step are clearly exposed in the DMP to gain an overview of the overall workflow of the Data Management Process. Thus, this key document needs to be signed off before commencing significant work.

This document is created by the Data Manager (DM) responsible for the study and will be reviewed and approved, at least, by the following people:

- Chief Investigators: Dr. Ignacio Herraiz García.
- Data Manager: Paula Mínguez Muñoz.
- Project Manager: Irene Llorente Muñoz.
- Biostatisticians: M. Carmen Romero Ferreiro.

The DMP will be saved and stored with the study documentation. Any changes performed in the Data Management Plan during its development should be identified by a new version number and the date of change. A copy of the new document will be sent to the sponsor for its review and approval.

# 2 STUDY CHARACTERISTICS.

## 2.1 Aim of the study

To evaluate through a clinical research study whether Cook's balloon cervical ripening for labor induction from 37+0 weeks of gestation in late IUGR (Intrauterine growth restriction) is able to increase the probability of vaginal delivery compared to the use of vaginal dinoprostone, without increasing neonatal morbidity.

## 2.2 Participating centres and their location

- Hospital Universitario 12 de Octubre (Madrid, Spain).
- Hospital Clínic i Provincial (Barcelona, Spain).
- Hospital Sant Joan de Déu (Barcelona, Spain).
- Hospital Clínico Universitario Virgen de la Arrixaca (Murcia, Spain)
- Hospital Universitari Vall d'Hebron (Barcelona, Spain)

## 2.3 Number of subjects

172 patients, 86 for each treatment group (experimental and control group).

# 3 GENERATION OF THE DATABASE AND DIFFERENT SOURCES OF DATA.

When Scientific Support Unit of i+12 provides Data Management support for a clinical trial which has been assigned through the SCReN node, the unit is in charge of building, managing and controlling its CDMA (Clinical Data Management Application). This CDMA includes not only the

eCRFs used to collect the data, but also the associated queries, reports, related files, validation checks, branching logic, etc. These CDMAs are built upon an underlying clinical database management system (CDMS), which is RedCap 8.7.4 for this project.

### 3.1 Study design.

The way in which the CDMA is designed is the starting point for successfully recording clinical trial data. The CDMA is built by prototyping, gradually building it in a series of incremental steps that make it easier to check that all specifications set on the protocol are being satisfied. Meanwhile, constant communication with the principal investigator/sponsor (mainly) is carried out. At the end of the CDMA design an annotated CRF will be sent to the PI/sponsor with the CDMA functional specifications under the name *CRF_COLIGROW*. These specifications will be generated from the final prototype and will include aspects such as: forms and their corresponding data entry fields, skipping and branching logic, calculated fields and data validation logic. This way it will be possible to ensure that CDMA specifications fully adapts to the specifications stablished by the protocol.

#### *3.1.1 CRF Changes.*

It may happen at some point, although it should not frequently happen, that a change is needed to be implemented to the CRF. This might be the case when the PI realizes that some field is causing confusion to data entry roles or that some form could be improved in some way. This implies a protocol amendment and also formally keeping track of the changes through new annotated CRF versions. Thus, whenever a change is implemented to the CDMA, the new annotated CRF must be sent to the PI/sponsor, who will certify by signature, that requested changes have been implemented and the new CRF version is approved.

### 3.2 Study management of users, roles and sites.

Moreover, as important as the CDMA organization itself, are the users who will make use of it, as well as their roles and the clinical sites they take part of. Users and roles (basic and data entry rights and privileges that users may have in the database) can be easily controlled through any of the CDMS we use. All these users have to be trained and, thus, familiar with the use of the CDMA before they can enter or deal with real data.

#### *3.2.1 User roles.*

These are the main roles that take part of a Project, and their corresponding responsibilities:

- Principal Investigator (PI): enrolls subjects, enters Data, answers/solves queries, and signs the casebook.
- Data Entry (DE): enrolls subjects, enters data, and answers/solves queries. The same permissions as Principal Investigator except for signing the casebook.
- Project Manager (PM): Views data, executes reports.
- Clinical Research Associate (CRA/Monitor): Views data, Source Data Verification (SDV) reviews, create queries, closes queries, and executes reports.
- Data Manager (DM): Views data, creates and closes queries opens and locks casebook, executes reports, manages database/CRF change requests.

For this specific Project, users and their corresponding roles will be specified in a separate document (*USERS_COLIGROW*). This document corresponds to an up-to-date list with the users of the project. This list will be reviewed from time to time to check that all users have the permits they are entitled to. At any time, all the users that are part of the project must have been previously trained to be familiar with the CDMA, otherwise they must not be able to introduce real data.

Moreover, activity that is carried out by users can be traced thanks to the *activity log* REDCap provides. All user activity for some range of time can be checked, accompanied with the timestamp of the executed action. Additionally, aggregate counts for activity can be seen.

#### *3.2.2 Data Access Groups.*

Apart from user roles, clinical sites to which users have to be assigned are equally relevant. In REDCap this site assignment is done through Data Access Groups (DAGs). For this project the different participating centers are assigned to different access groups as follows:

| **Site** | **DAG** |
|---|---|
| Hospital Universitario 12 de Octubre | 01 |
| Hospital Clínic i Provincial | 02 |
| Hospital Sant Joan de Déu | 03 |
| Vall d'Hebron | 04 |
| Virgen de la Arrixaca | 05 |

Users assigned to a DAG will be able to do the tasks they are enrolled to only for the records coming from the site they pertain to.

### 3.3 External sources.

Also, it has to be considered that for some projects the user will need to be familiar with external sources from which they have to obtain some response for lately introducing it in some form. This might be the case to questionnaires, calculators, etc.

For this Project a link to an online calculator for fetal variables is set in some fields, for which the user will have to introduce a value that is externally calculated.

### 3.4 Storage of data.

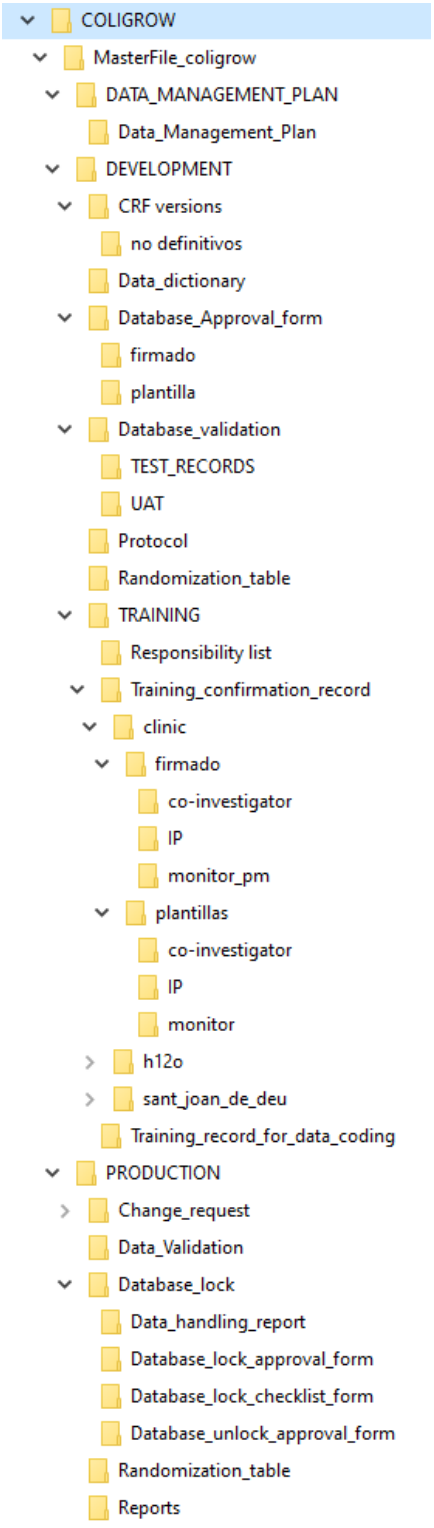
#### *3.4.1 Data archive specifications.*

All the documents to be generated during the whole Data Management process will be stored in the Master File of the Project. This Master File is organized in three separate files, one for the development phase, one for the production phase and one for the Data Management Plan itself. In the Development file documents regarding CRF versions, data dictionary, database approval form, database validation, the protocol, the randomization template and the training-related documents will be

stored. In the production file documents regarding change requests, data cleaning/validation, database lock and reports will be stored. This folders may contain documents that:

a) are downloaded from the CDMA.
b) are obtained through a direct information exchange with the CDMA via API.
c) are written by i+12 and filled and signed manually at a later time.

The folder structure is the following:


COLIGROW
MasterFile_coligrow
DATA_MANAGEMENT_PLAN
Data_Management_Plan
DEVELOPMENT
CRF versions
no definitivos
Data_dictionary
Database_Approval_form
firmado
plantilla
Database_validation
TEST_RECORDS
UAT
Protocol
Randomization_table
TRAINING
Responsibility list
Training_confirmation_record
clinic
firmado
co-investigator
IP
monitor_pm
plantillas
co-investigator
IP
monitor
h12o
sant_joan_de_deu
Training_record_for_data_coding
PRODUCTION
Change_request
Data_Validation
Database_lock
Data_handling_report
Database_lock_approval_form
Database_lock_checklist_form
Database_unlock_approval_form
Randomization_table
Reports

### *3.4.2 Long-term storage*

The Data Manager gathers all the documentation within 30 days after the acceptance of the final analysis by Chief Investigator/Sponsor. All study documents will be then sent to the Sponsor, who will be also asked to fill an acknowledgment of receipt once the inventory is complete.

The Chief Investigator/Sponsor should retain the contents of the master file in paper or digital format for each clinical trial for at least twenty-five years after the end of the trial (according with current national legislation) or for a longer period if other applicable requirements. The sponsor is responsible of the destruction of the documents and files once the correspondent period of time according with current national legislation or for a longer period if other applicable requirements has expired.

### *3.4.3 Physical storage of data.*

All data collected by RedCap eCRFS is stored in a relational database system called MySQL. Specifically, it is stored in the database "c2redcap2" and in the table "redcap_data" whose structure is the following:

```
+------------+--------------+------+-----+---------+-------+
| Field      | Type         | Null | Key | Default | Extra |
+------------+--------------+------+-----+---------+-------+
| project_id | int(10)      | NO   | MUL | 0       |       |
| event_id   | int(10)      | YES  | MUL | NULL    |       |
| record     | varchar(100) | YES  |     | NULL    |       |
| field_name | varchar(100) | YES  |     | NULL    |       |
| value      | text         | YES  |     | NULL    |       |
| instance   | smallint(4)  | YES  |     | NULL    |       |
+------------+--------------+------+-----+---------+-------+
```

The server where this database runs is a Debian-GNU/Linux virtual machine hosted on a VMWare virtualization node.

## 4 RANDOMIZATION.

Patients will be randomly assigned to control or experimental group. The randomization table used to carry out this process is designed with SAS by Biostatistics of our team to ensure that the distribution of the groups is balanced. This table is saved under the name *RandomizationTable_COLIGROW*.

This randomization table (called allocation table by REDCap) is loaded into the CDMA. We use the DAGs to randomize according to the site of origin, and assign the randomization result to the

random variable. This last field of the form will then show for each record to which treatment group it has been assigned.

## 5 TRAINING.

User training will focus on navigation through forms and understanding of data entry workflow. A video with all the needed instructions for using the CDMA will be recorded by the DM and provided for all those users which are going to use it at a later time. Also, roles will be created for making it possible to the users to try out the functioning of the CDMA on the test environment.

After being provided with the training recording, users will check it out and ask the DM, if needed, any doubt that may arise to them while trying out the CDMA. After this period, once they consider they are sufficiently trained to comfortably use the CDMA, they will sign the training confirmation record.

Once this training confirmation is received, users will be included in the production CDMA, the environment which deals with real data: patient records. Each user will be added to the production CDMA with its corresponding role.

## 6 DATA VALIDATION PLAN AND DATA QUALITY RULES.

In REDCap, some data quality rules are set by default, such as: missing values (for every field or for required fields only), field validation errors (for incorrect data type or for out of range values), outliers for numerical fields, hidden fields that contain values, multiple choice fields with invalid values and incorrect values for calculated fields.

Some of these evident quality rules are actually data entry checks that need to be programmed in such a way that obvious errors are immediately asked to be corrected through system pop-ups. Thus, during the CRF design it is important to correctly set all the validation fields we want to be applied during data entry. This way, self-evident corrections (SECs) are automatically displayed as a suggestion of change for the data entry user. These pop-ups could alert, for example, of evident omission, addition or transposition of data.

However, if a guarantee of the highest data quality is pursued, apart from the previously mentioned quality rules, extra rules need to be specifically constructed for each individual Project.

A list of the data quality rules implemented in this specific project is found in *DQR_COLIGROW* (attachement A).

To guarantee the optimal quality of data, not only validation checks and self-built data quality rules are needed, but also the ability to correct the errors or alerts these quality measures may arise when introducing real data.

In REDCap, this follow-up can be done through the “data resolution workflow”. This module provides an easy way to manage and document the so-called data queries. It is worth mentioning

that this module not only provides the possibility to generate queries, but also to verify the values entered in each form, duty that is assigned to the monitor.

This module must be activated at a project level if wanted. After activating the module, the "user rights" must be modified, giving the ability to "respond only to open queries" to the "data entry" users, and the ability to "Open, close and respond to queries" to the DM and the Monitor.

The general process would be:

1) Identification of an “issue” and query opening. DM or CRA can open this query via a) data entry form (by clicking on the yellow pop-up next to each field) or by b) individually executing each data quality rule. Also, each query can be sent to an specific user if needed.
2) Investigator replies to the opend query by solving the issue and preferably adding an explanatory comment.
3) Resolution of the issue is checked by the user who opened it (DM or CRA) and checks whether the query should be closed.

The whole thread of what happened right in one field can be seen by clicking on the data resolution workflow pop-up. Also, from the resolve issues page all the queries can be seen, tracked and even exported if needed (which allows, for example, to generate reports of missing or late data).

Moreover, Resolution Metrics can be observed in the resolution metrics page, where information regarding the amount of open or close queries, the average time queries remain unresolved, average time for query response, average time for query resolution, and some more, can be found, even stratifying by DAG activity. This can help to optimize aspects such as the more queried fields or the more queried data quality rules.

### 6.1 Schedule of checks.

Data cleansing activities include manual data reviews and automated checks that identify inaccurate or invalid data, missing data, protocol deviations, and consistency checks.
These checks will be performed every 10 patients included by CRF.

## 7 REPORTS.

Once data wants to be exported, all records and fields can be downloaded together, which is probably what will be needed since the study design considered all the variables to be important for further analysis. Nevertheless, it is also possible to obtain more customized reports, in which specific instruments and events can be chosen, and filters can be applied, for example considering some advanced logic.

This can be interesting for example if data is needed for possible secondary re-use, assuming study participants' consent allows this.

### 7.1 De-identification/deletion of data.

For this particular study the statistical analysis of data will be performed in a blinded manner to limit possible assessment bias. The previous statement means that the treatment group in which the patient is allocated will remain unknown to the statistician.

## 8 DATA CODING.

Data coding will be carried out once all data has been collected or during data collection after data verification. The data manager is the responsible of doing so, and if coding is performed, the coding list will be sent to the principal investigator for him/her to check it and approve it. If new versions of dictionaries appear in the course of the project, principal investigator will be notified and actions to be implemented will be discussed. For this exact project, coding is not performed, so this point does not apply.

## 9 SERIOUS ADVERSE EVENTS (SAEs) RECONCILIATION.

The SCReN standard for SAE reconciliation will be to reconcile CRF data with the SAE database listings. A scheduled communication timeline between the Data Manager and the Pharmacovigilance node will be stablished every depending on the number of serious adverse events occurred, in order to perform the SAE reconciliation along the study, as it is important to verify the follow up of these events and always before the database closure.

The Pharmacovigilance node will send, in the accorded scheduled time, a report of the SAE included in their SAE database to de Data Manager, in order to carry out their reconciliation. Data Management will verify the following variables to either an exact match (data should be exactly the same) or consistency of data (data should have the same meaning but may be stated in different words):

1. Project code (exact match)
2. Investigator number (exact match)
3. Subject Identifier Information (exact match)
4. Patient details (Gender, Age and Date of Birth, Race)
5. Event Start/End Dates (consistent)
6. Reported Term for the Adverse Event (consistent)
9. Outcome (exact match)

Discrepancies found between SAE Listing will be clarified with the safety contact, in the following way:

1. If the result of the comparison indicates that more SAEs have been entered into the clinical database than have been entered into the safety database, the DM will contact with the safety database contact to obtain the missing SAE information for the safety database.

2. If the result of the comparison indicates that more SAEs have been entered into the safety database than have been entered into the clinical database, the DM issues a query to the Investigator requesting the missing SAE information.

3. If the result of the comparison indicates a difference in a specific value entered into the two databases, the DM and the safety database contact determine if a data entry error has occurred:

- If no data entry error has occurred, the DM will issue a query to the Investigator.

- If the Investigator indicates that the clinical database contains the correct data, the DM will communicate this to the safety database contact.

- If the Investigator indicates that the information entered into the clinical database is not correct, the DM will ask the Investigator to update that information in the clinical database.

## 10 DATABASE LOCK.

Once validation, SAE reconciliation and all coding activities have been completed and the database has been verified by the monitor, the database will be locked. The study database must be locked by software and hardware to ensure its integrity for results generation, analysis and submission. When the collection and review of the study data is finally completed all electronic or paper documentation will be sent to the trial sponsor with acknowledgement of receipt to be stored for the time established by legislation.

Once the database is locked, the data manager will produce an Adobe® PDF document format of the electronic eCRFs which will be sent to participating sites and the study sponsor. Software locking of the database must be performed prior to any analysis or interim report from which regulatory or testing decisions will be made. Soft locking of the study will begin once all applicable eCRF forms, queries or documents for subjects are correctly processed following the Data Management Plan and corresponding Standard Operating Procedures, which also means that all subjects are declared clean and the correct steps were followed.

The Data Manager will complete the Data Handling Report and distribute it for review/revision. Once chief Investigator signs it, completion of the study is achieved, meaning that all tasks are completed and approval signatures are obtained. Then, all study books will be locked in the eCRF.

The Lockout form will be distributed to the Biostatistician, Project Manager, and Chief Investigator.

The Data Manager will conduct a final inventory of all data management documentation and the study database will be returned to the sponsor within 30 days having accepted the final analysis. All study documents will be returned to the developer with acknowledgement of receipt upon completion of the inventory.

Once the study is closed, all information will be retained in the data management files until all documentation is returned and no copies of the documentation will be stored, so any requests related to the study will have to be made during this period. The developer is responsible for the destruction of documents and files.

## 11 DATA TRANSFER.

The data manager will prepare a file in SAS with the data ensuring that statistical analyses of the study data will be performed in a blinded manner by a third party to limit possible evaluation bias. Data will always be encrypted and transferred in a password-protected zip file that includes a data acknowledgement (to be signed by the recipient-biostatistician) and a transfer query report (to be completed in case a discrepancy is found in the transfer).

While the study is in production, each data transfer request must be communicated in writing to the sender. The recipient will then receive a transfer with actual patient data in the selected program datasets in accordance with the annotated eCRF and should review the data and confirm that it has been received correctly or report any discrepancies. The Data Manager shall correct any eventual errors in the transfer process until the data is correctly submitted. The Data Manager will record the transferred data sets in the study directory accompanied by all related documentation.

Data for final statistical analysis will be transferred only once the database is locked. The data transfer will be repeated if any changes to the database are needed after the database is locked.

The established transfer schedule will be: A first data transfer will be performed in a first stage when the completion of the study is reached in 88 pregnant women, 44 in each branch, which will correspond to approximately 13 months, and that is where an intermediate statistical analysis will be performed. At a later time, a second data transfer will be performed, at approximately 26 months, which corresponds to the end of the study.

## Supplemental material 2: Statistical analysis plan

# Statistical Analysis Plan

## Title:

Cook´s balloon versus dinoprostone for Labour Induction of term pregnancies with fetal GROWth restriction (COLIGROW study)

## Protocol version

Version 1.1. Date: 18/ 05/ 2023

Protocolo COLIGROW v1.1_2023-05-18.pdf

## Data capture version

Version 1.0. Date: 21/02/ 2023

CRF_APPROVAL_FORM_COLIGROW_v1_IHG_PMM_ILM_CRF.pdf

## Signature:

| USCI Hospital Universitario 12 de Octubre |
|---|
| Name:<br>_Cristina Martín-Arriscado Arroba_<br>_Carmen Romero Ferreiro_<br>_David Lora Pablos _<br>Date: _21_ /_JUN_ /_2023_ |

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## Contents

# 1 Introduction

Fetal growth restriction (FGR) is a situation in which the fetus fails to reach its intrinsic growth potential, usually due to placental insufficiency [1]. Late-onset forms of FGR (diagnosed >32 weeks) are the most prevalent (70-80%). The greatest risk for these fetuses with late-onset FGR appears once they reach term, when other stressful situations are added to their situation of relative hypoxia, such as the appearance of contractions and funicular compression. Thus, it has been shown that from 37-38 weeks the risk of stillbirth increases [2] and it is advised not to exceed this threshold to indicate the induction of labour [3,4].

Detection of late-onset FGR is not easy in clinical practice. A key aspect is to differentiate it from the constitutionally small for gestational age (SGA) fetus, whose prognosis is similar to that of the general population. In this sense, the role of Doppler patterns of hemodynamic deterioration to differentiate between SGA and late-onset FGR have been extensively investigated [5]. Thus, it has been observed that in late-onset FGR the degree of malnutrition is lower, and the hemodynamic alterations are usually more subtle as a consequence of a milder placental insufficiency. This means that most cases of late-onset FGR remain with anterograde umbilical artery (UA) flow [4]. However, as the pregnancy reaches its term, fetal respiratory demands increase exponentially and tolerance to hypoxia is lower, which in the hemodynamic study of the fetus is expressed as a redistribution of flows towards the brain territory to prioritize its oxygenation. The Doppler parameter that best reflects this phenomenon of brain-sparing is the cerebroplacental ratio (CPR), which results from dividing the resistance in the middle cerebral artery (MCA) by the resistance in the UA. To date, a broad consensus has already been achieved among experts to use CPR < 5th percentile as a diagnostic criterion for late FGR [6]. Furthermore, in our experience5 and that of others [7], the presence of a CPR < 5th percentile in term FGR foetuses is associated with fetal distress during labour and worse perinatal outcomes.

Attempting a vaginal birth through labour induction is by consensus the most reasonable option among pregnancies complicated with late-onset stage I FGR [8], taking into account the multiple advantages of the vaginal route over an elective caesarean section. In the case of FGR, some of these benefits are especially relevant for the health of the newborn whose growth has been restricted in intrauterine life, such as the facilitation of skin-to-skin contact and the early initiation of breastfeeding [9].

Induction of labour in late-onset FGR presents good results in terms of achieving a vaginal delivery, although these fetuses have an increased risk of caesarean section due to fetal distress. Since mechanical methods for cervical ripening in the first phase of labour induction (Foley catheter and Cook´s balloon) are associated with less uterine stimulation with a lower rate of tachysystole than prostaglandins, they have been proposed as suitable for cervical ripening in FGR, since they could reduce the risk of fetal distres [10,11]. Our observations support this hypothesis: in a “before and after” retrospective study on 148 cases of singleton pregnancies with late-onset FGR stage I undergoing induction of labour with cervical ripening, the percentage of caesarean sections due to suspected fetal distress decreased after switching from vaginal dinoprostone to mechanical methods (26.0% vs. 7.0%, p < 0.01) [12]. However, these promising results they must be endorsed by a randomized clinical study to evaluate the impact on clinical

practice. To our knowledge, this will be the first clinical research study that compares cervical ripening using mechanical methods (Cook's balloon) with cervical ripening using pharmacological methods (vaginal dinoprostone) for the induction of full-term singleton pregnancies complicated with FGR. This will cover the current lack of knowledge about what is the most suitable method to perform cervical ripening in this population.

# 2 Hypothesis and objetives

## 2.1 Aim hypothesis

In the induction of labour for late-onset stage I FGR, cervical ripening with Cook's balloon obtains a higher percentage of vaginal deliveries than ripening with vaginal dinoprostone, safely for the mother and the newborn.

- Null hypothesis (H0): percentage of vaginal birth with Cook´s balloon ≤ percentage of vaginal birth with vaginal dinoprostone.
- Alternative hypothesis (H1): percentage of vaginal birth with Cook´s balloon > percentage of vaginal birth with vaginal dinoprostone.

## 2.2 Main objetives

### 2.2.1 Primary objective

To evaluate, through a clinical research study, whether cervical ripening with a Cook´s balloon for the induction of labour from 37+0 weeks of gestation in the late-onset FGR manages to increase the rate of vaginal delivery compared to the use of vaginal dinoprostone, without increasing neonatal morbidity.

## 2.3 Secondary objectives

### 2.3.1 Effectiveness

1. To compare the percentage of caesarean sections due to suspected fetal distress.
2. To analyze the mean time interval between the onset of cervical ripening and delivery.

### 2.3.2 Safety

To evaluate the neonatal morbidity through the MAIN (morbidity assessment index for newborns) score, presence of neonatal acidosis, and neonatal intensive care unit (NICU) admission.

### 2.3.3 Satisfaction

To assess the maternal satisfaction through the Mackey childbirth satisfaction rating scale.

# 3 Study Design

## 3.1 Description of the clinical trial

Clinical research study with a medical device that is CE marked and used for its intended purpose. This is a multicenter, prospective, randomized, open study of parallel groups, in which patients will be randomized in a 1:1 ratio, to evaluate the efficacy and safety of the Cook balloon in pregnant women with a singleton pregnancy and a fetus diagnosed prenatally of FGR in stage I with indication of termination of pregnancy by induction of labour with an unfavorable cervix at the beginning and, therefore, susceptible to the use of a cervical ripening method as an alternative to standard treatment with dinoprostone, administered vaginally.

The study plans to carry out an interim analysis when the number of 88 pregnant women with all their visits completed is reached, 44 in each arm, which is expected to happen approximately 13 months after recruitment begins.

### 3.1.1 Study Intervention(s) Administered

**Group 1 (experimental):** Cook´s Cervical Ripening Balloon with Adjustable Stylet®, Ref: J-CRBS-184000. The device consists of a silicone double balloon catheter and a malleable stylet of adjustable length. The maximum inflation of the balloon is 80ml/balloon of serum.

**Grupo 2 (control):** PROPESS 10 mg vaginal delivery system consisting of a non-biodegradable polymeric drug release device containing 10 mg of dinoprostone (Prostaglandin E2) dispersed in the matrix. Vaginal dinoprostone will be used as it is the standard treatment.

## 3.2 Randomization

The randomization list will be generated using software SAS 9 for Windows. The randomization list will be imported into the REDCap program so the researchers can randomize candidate subjects using an easier-to-use interface. Subjects that meet the selection criteria will be randomized in a 1:1 ratio between the two treatment groups in blocks of 6, stratifying by center. The assignment of treatment to each subject will be centralized, keeping the sequence hidden.

### 3.2.1 Blinding

This clinical research study is open, both the patient and the researcher will know the treatment assignment group, because both the active comparator drug (vaginal dinoprostone) and the medical device of the experimental group (Cook's balloon) are easily recognizable both. for the researcher as well as for the patient. It is unlikely that the open nature of the study could produce a bias that significantly affects the evaluation of the main variable of the study: vaginal delivery.

## 3.3 Sample size

The sample size necessary to evaluate that cervical ripening with Cook's balloon for the induction of labour from week 37+0 of gestation in singleton pregnancies with late-onset stage I FGR manages to increase the rate of vaginal delivery compared to the use of vaginal dinoprostone, assuming that the vaginal delivery rate was 62.3% with prostaglandins versus 84.5% with mechanical methods [12], in a one-sided test (H1) with early stopping to reject or accept H0 at an alpha level of 0.025 and statistical power of 90% with 2-stage sequential design

using the O'Brien-Fleming method, with 1:1 treatment assignment, will be a total of 162 women, 81 pregnant in each group. Due to possible losses, the sample will be increased by 5% and will consist of a total of 172 women, 86 pregnant in each group.

The programming code and the result appear in the section of the appendix called Sample size.

## 3.4 Interim analysis

A sequential design will be used to stop the trial early for effectiveness of cervical ripening with Cook's balloon on the percentage of vaginal birth versus the percentage of vaginal birth with vaginal dinoprostone cervical ripening. The sequential design will use the O'Brien-Fleming method for two stages, with a starting alpha level equal to 0.025, and will use a unilateral alternative hypothesis (H1) with an early stop to reject or accept the null hypothesis (H0). The first stage will be carried out when the study is completed in 88 pregnant women, 44 in each branch, which will correspond approximately to 13 months, and will have the following scheme:

1. If the Z statistic ≥ 2.767, then H0 is rejected and the study is stopped
2. If Z statistic < 0.437, then H0 is accepted and the study is stopped
3. In any other case, the study continues

The second stage will coincide with the end of the study (approximately 26 months), 172 pregnant women, 86 in each group. It will be evaluated as follows:

1. If Z statistic >= 1.957, then H0 is rejected
2. If Z statistic < 1.957, then H0 is accepted.

The number of pregnant women in the intermediate and global analysis includes the increase in patients due to possible losses.

The results obtained in the interim analysis will be presented to the Promoter, who must notify the researchers, the center, the local Drug Research Ethics Committee (CEIm) and the Spanish Agency for Medicines and Health Products (AEMPS).

## 3.5 Scope of study and time frame

The clinical trial will be carried out in 5 centers in Spain: Hospital 12 de Octubre, Hospital Clinic i Provincial, Hospital Sant Joan De Déu, Hospital Vall d´Hebron, Hospital Virgen de la Arrixaca.

After obtaining study approvals from the CEIm and AEMPS and signing contracts with the centers, the schedule is as follows:

- Estimated recruitment period: 26 months
- Duration of patient treatment: 1 day
- Follow-up period for each patient: while the patient is hospitalized, it is usual for follow-up to be carried out from day 3 to 5 after randomization and induction of labour.
- Analysis of results, preparation of the final report and publication of results: 4 months

## 3.6 Study population

Pregnant women with a singleton pregnancy and a fetus prenatally diagnosed with stage I FGR, with an obstetric indication for planned term delivery by induction of labour and an unfavorable cervix.

## 3.7 Inclusion and exclusion criteria

### 3.7.1 Inclusion criteria

Patients must meet the following inclusion criteria:

- Singleton pregnancy
- Age ≥ 18 years
- Gestational age (GA) dated by first trimester ultrasound ≥ 37+0 weeks at the onset of labour induction
- Cephalic presentation
- Stage I FGR, defined as the presence of at least one of these two criteria:
    - Estimated fetal weight (EFW) < 3rd percentile
    - EFW < 10th percentile and at least one of the following:
        - Umbilical artery pulsatility index > 95th percentile (and presence of antegrade end-diastolic flow) or
        - CPR < 5th percentile
- Bishop score < 7
- Intact fetal membranes
- No previous cesarean section
- No maternal or fetal contraindications for vaginal delivery or induction of labour.

### 3.7.2 Exclusion criteria

Pregnant women who have been diagnosed with any of the following criteria will not be considered candidates to participate in the study, so they will not be able to participate in the study:

- Major fetal malformation
- Fetal genetic abnormality
- Fetal congenital infection

## 3.8 Ethics Committee Approval

The study protocol was evaluated and approved by the CEIm of the Hospital Universitario 12 de Octubre and AEMPS, whose protocol code is 21/728.

## 3.9 Additional considerations

Recruitment will be competitive, it is estimated that the coordinating center (Hospital 12 de Octubre) will be able to recruit 50 patients, the Hospital Clinic i Provincial 50 patients, the Hospital Vall d´Hebron 25 patients, the Hospital Virgen de la Arrixaca 25 patients and the Hospital Sant Joan de Deu 22 patients.

# 4 Statistical analysis

## 4.1 General considerations

All analyses will be carried out using the program applied to SAS statistics, version 9 of the SAS system for Windows.

At the end of the study, descriptive summaries of the demographic variables and other characteristics of the subjects specified in the electronic case report form (eCRD) will be made based on the two treatment groups. Unless otherwise specified, all continuous variables will be summarized using the number of patients (n), mean, standard deviation, median, minimum and maximum. Categorical variables will be described by absolute and relative frequency.

## 4.2 Analysis sets

The efficacy analysis will be performed in the intention-to-treat population. All randomized patients will be included in the intention-to-treat analysis and will be classified according to the assigned treatment group, regardless of the treatment received and whether they have received it.

All pregnant women who receive at least 1 dose of the study intervention, that is, in whom one of the cervical ripening methods has been inserted, will be included in the safety and satisfaction analysis.

The per-protocol population is considered to be all pregnant women who receive at least one dose of the assigned study treatment, duly complying with the protocol criteria (inclusion/exclusion) and following the instructions of the trial protocol. That is, pregnant women who have been included in the study and have not incurred major deviations from the protocol during the study.

## 4.3 Participant flowchart

The flowchart of progress through the phases of the COLIGROW clinical trial will be designed following the CONSORT guideline [13,14].

## 4.4 Baseline characteristics

Baseline characteristics corresponding to the screening visit will be disaggregated according to the allocation group by demographic data, risk factors and history. Also, the data from the pre-treatment visit will be described depending on the allocation group. Continuous variables will be summarized using the number of patients (n), mean, standard deviation. If the normality test (Kolmogorov-Smirnov test) is rejected, they will be described using the median along with the 25th and 75th percentile. Categorical variables will be described using the absolute and relative frequency. Likewise, the baseline visit will be described by assignment group.

## 4.5 Evaluation of study objectives

### 4.5.1 Effectiveness objectives

#### *4.5.1.1 Primary effectiveness objective*

The main objective of effectiveness will be carried out through the unilateral test (one-tailed test) of the chi-square and alpha error equal to 0.025 to evaluate that cervical ripening with

Cook's balloon obtains a higher percentage of vaginal deliveries than ripening with vaginal dinoprostone. The 95%CI of the difference in proportions will also be provided.

```
proc freq data= BaseEnsayoClinico;

        tables cesareas*tratamiento /chisq  alpha=0.025;

run;
```

#### *4.5.1.2 Secondary efficacy objectives*

Secondary efficacy objectives to evaluate:

- percentage of cesarean sections due to fetal distress,
- percentages of achievement of cervical ripening (Bishop score ≥ 7),
- frequency of occurrence of episodes of uterine hyperstimulation, defined as tachysystole (>5 contractions/10 minutes) with fetal repercussions (alteration of CTG), during the latent phase,
- frequency of occurrence of episodes of uterine hyperstimulation, defined as tachysystole (>5 contractions/10 minutes) with fetal repercussions (alteration of the CTG), during the active phase

between cervical ripening with Cook's balloon versus cervical ripening with vaginal dinoprostone will be carried out through the two-tailed chi-square test (bilateral) and alpha error equal to 0.05.

On the other hand, the study of the duration of the latent phase (from the beginning of induction to the beginning of the active phase) and duration of labour from the beginning of the active phase (4 cm and 90% effacement or 5 cm regardless of effacement, 2 painful contractions/10 min) between both study groups will be carried out using a two-tailed t-test and alpha error equal to 0.05, after evaluating the normality hypothesis with the Kolmogorov-Smirnov test. If the normality hypothesis is rejected, a Mann-Whitney-Wilcoxon test will be performed for two samples.

```
proc freq data= BaseEnsayoClinico;

        tables cesareas*tratamiento /chisq;

run;

proc ttest data= BaseEnsayoClinico plots(unpack)=summary;

        class tratamiento;

        var tiempo;

run;
```

The evolution of the level of satisfaction at hospital discharge, assessed according to the Spanish version of the “Mackey childbirth satisfaction rating scale” between those pregnant women with cervical ripening with Cook's balloon and pregnant women with cervical ripening with vaginal

dinoprostone will be carried out through a two-tailed t-test and alpha error equal to 0.05. If the normality hypothesis is rejected (Kolmogorv-Smirnov test), a Mann-Whitney-Wilcoxon test will be performed for two samples.

### 4.5.2 Safety aim

The safety objectives will be carried out through the two-tailed chi-square test and alpha error equal to 0.05 or the Fisher exact test to evaluate the maternal safety parameters (percentages of intrapartum maternal fever; percentages of dystocia of shoulders and percentages of severe maternal morbidity) and fetal (percentages of neonatal acidosis, percentages of Apgar score at 5 minutes < 7 and percentages of admission to the NICU) between the two groups.

The evaluation of the MAIN score of neonatal morbidity between those pregnant women with cervical ripening with Cook's balloon and pregnant women with cervical ripening with vaginal dinoprostone will be carried out through a two-tailed t-test and alpha error equal to 0.05. If the normality hypothesis is rejected (Kolmogorv-Smirnov test), a Mann-Whitney-Wilcoxon test will be performed for two samples.

```
proc freq data= BaseEnsayoClinico;
        tables (Acidosis Ingresos)*tratamiento /chisq;
run;


proc ttest data= BaseEnsayoClinico plots(unpack)=summary;
        class tratamiento;
        var MAIN;
run;
```

## 4.6 Interim analysis

Interim analysis will be studied bellow Interim analysis

## 4.7 Procedures used to account for lost, unused and erroneous data

No imputation procedure will be carried out on the study variables, although the origin of the missing data will be studied in relation to the follow-up of the patients and their evolution. The missing information in the objective variables will be quantified in absolute frequency and shown with respect to the total number of subjects per treatment arm. The information available for each subject will be used.

## 4.8 Additional considerations

Subgroup analysis is not contemplated.

# 5 Glossary

| | |
|---|---|
| AEMPS | Spanish Agency for Medicines and Health Products |
| CEIm | Drug Research Ethics Committee |
| CPR | Cerebroplacental ratio |
| CTG | Cardiotocography |
| eCRD | Electronic case repord form |
| EFW | Estimated fetal weight |
| FGR | Fetal Growth Restriction |
| GA | Gestational age |
| H0 | Null hypothesis |
| H1 | Alternative hypothesis |
| MAIN | Morbidity Assessment Index for Newborns |
| MCA | Middle cerebral artery |
| NICU | Neonatal Intensive Care Unit |
| SGA | Small for gestational age |
| UA | Umbilical Artery |

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# 7 Appendix

## 7.1 Sample size

### 7.1.1 Programming code

The results and code for sample size were generated using the SAS software (Copyright © [2002-2012] by SAS Institute Inc., Cary, NC, USA).

```
proc seqdesign altref=0.222; *0.845 - 0.623;
      OneSidedOBrienFleming: design nstages=2
      method=obf alt=upper stop=both
      alpha=0.025 beta=0.10;
      samplesize model(ceiladjdesign=include)
      =twosamplefreq(nullprop=0.623 test=prop);
      ods output AdjustedBoundary=Bnd_Prop;
run;

proc seqtest Boundary=Bnd_Prop errspend;
run;
```

### 7.1.2 Results

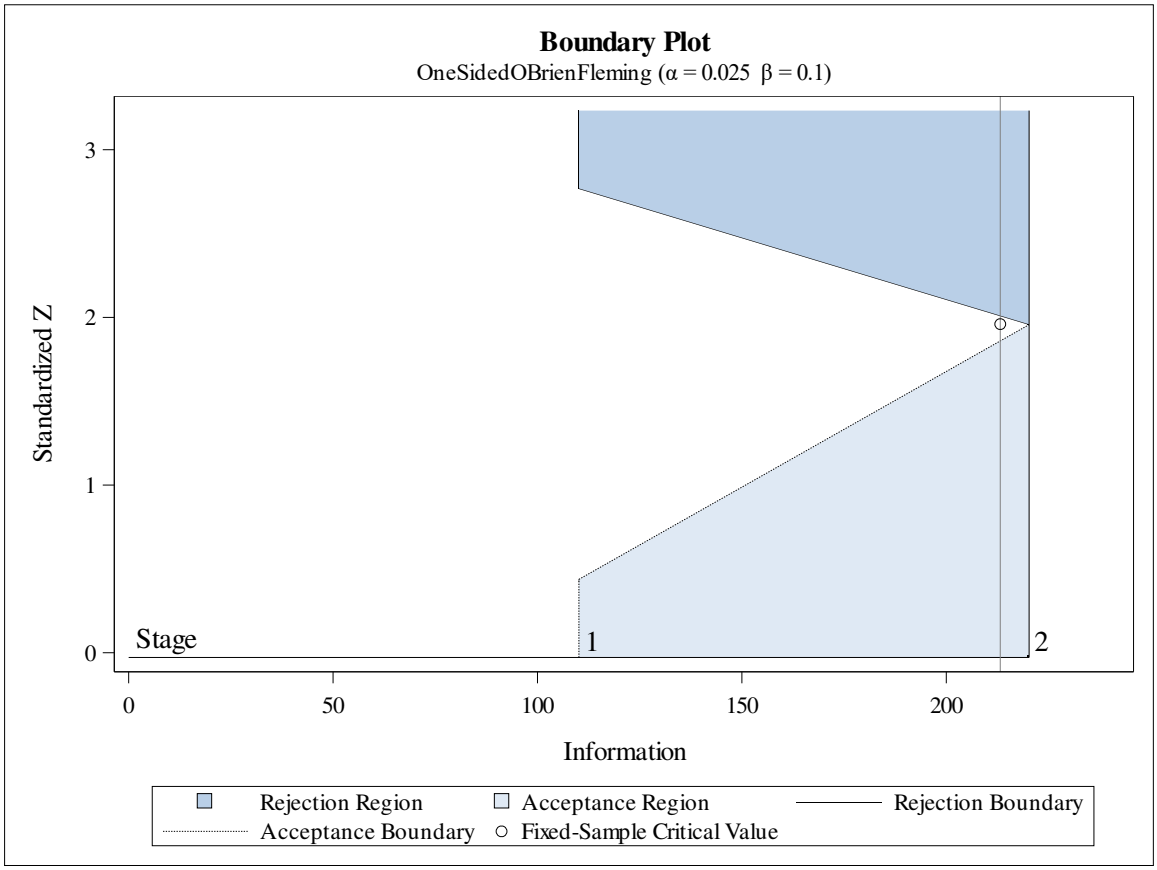
***The SEQDESIGN Procedure***
***Design: OneSidedOBrienFleming***

| Design Information | |
|---|---|
| **Statistic Distribution** | Normal |
| **Boundary Scale** | Standardized Z |
| **Alternative Hypothesis** | Upper |
| **Early Stop** | Accept/Reject Null |
| **Method** | O'Brien-Fleming |
| **Boundary Key** | Both |
| **Alternative Reference** | 0.222 |
| **Number of Stages** | 2 |
| **Alpha** | 0.025 |
| **Beta** | 0.1 |
| **Power** | 0.9 |
| **Max Information (Percent of Fixed Sample)** | 103.3104 |
| **Max Information** | 220.2593 |
| **Null Ref ASN (Percent of Fixed Sample)** | 68.5966 |
| **Alt Ref ASN (Percent of Fixed Sample)** | 84.71245 |
| **Adj Design Alpha** | 0.025 |
| **Adj Design Beta** | 0.09864 |

| Design Information | |
|---|---|
| **Adj Design Power** | 0.90136 |
| **Adj Design Max Information (Percent of Fixed Sample)** | 103.3519 |
| **Adj Design Max Information** | 221.4046 |
| **Adj Design Null Ref ASN (Percent of Fixed Sample)** | 68.66132 |
| **Adj Design Alt Ref ASN (Percent of Fixed Sample)** | 84.29504 |

| Method Information | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Unified Family | | | | |
| **Boundary** | **Method** | **Alpha** | **Beta** | **Rho** | **Tau** | **C** | **Alternative Reference** | **Drift** |
| Upper Alpha | O'Brien-Fleming | 0.02500 | . | 0.5 | 0 | 1.95688 | 0.222 | 3.294732 |
| Upper Beta | O'Brien-Fleming | . | 0.10000 | 0.5 | 0 | 1.33785 | 0.222 | 3.294732 |

| Boundary Information (Standardized Z Scale)<br>Null Reference = 0 | | | | | | |
|---|---|---|---|---|---|---|
| | | | | Alternative | Boundary Values | |
| | Information Level | | | Reference | Upper | |
| **_Stage_** | **Proportion** | **Actual** | **N** | **Upper** | **Beta** | **Alpha** |
| 1 | 0.5000 | 110.1297 | 80.581 | 2.32973 | 0.43772 | 2.76744 |
| 2 | 1.0000 | 220.2593 | 161.162 | 3.29473 | 1.95688 | 1.95688 |




| Sample Size Summary | |
|---|---|
| **Test** | Two-Sample Proportions |
| **Null Proportion** | 0.623 |
| **Proportion (Group A)** | 0.845 |
| **Test Statistic** | Z for Proportion |
| **Reference Proportions** | Alt Ref |
| **Max Sample Size** | 161.162 |
| **Expected Sample Size (Null Ref)** | 107.0092 |
| **Expected Sample Size (Alt Ref)** | 132.1496 |

| Sample Sizes (N)<br>Two-Sample Z Test for Proportion Difference | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Fractional N | | | | Ceiling N | | | |
| _Stage_ | N | N(Grp 1) | N(Grp 2) | Information | N | N(Grp 1) | N(Grp 2) | Information |
| 1 | 80.58 | 40.29 | 40.29 | 110.1 | 82 | 41 | 41 | 112.1 |
| 2 | 161.16 | 80.58 | 80.58 | 220.3 | 162 | 81 | 81 | 221.4 |

| Ceiling-Adjusted Design Boundary Information (Standardized Z Scale)<br>Null Reference = 0 | | | | | | |
|---|---|---|---|---|---|---|
| | | | | Alternative | Boundary Values | |
| | Information Level | | | Reference | Upper | |
| _Stage_ | Proportion | Actual | N | Upper | Beta | Alpha |
| 1 | 0.5062 | 112.069 | 82 | 2.35015 | 0.45859 | 2.75142 |
| 2 | 1.0000 | 221.4046 | 162 | 3.30329 | 1.95752 | 1.95752 |

**NOTE 1**: The output of proc seqtest is not displayed
**NOTE 2:** This was considered a one-tailed test, given that vaginal dinoprostone is a treatment considered standard therapy in many centers.

## 7.2 SATISFACTION SURVEY: MACKEY SCALE

POR FAVOR, SEÑALE SU GRADO DE SATISFACCIÓN CON CADA UNO DE LOS ASPECTOS QUE SE NOMBRAN A CONTINUACIÓN, TENIENDO EN CUENTA QUE EL 1 ES MUY INSATISFECHA. EL PUNTO MEDIO, ES DECIR EL 3, SIGNIFICA QUE NO PUEDE VALORAR ESE ASPECTO PORQUE NO SE HA PRODUCIDO EN SU PARTO (por ejemplo, el apoyo del acompañante si no ha estado acompañada, o la atención del ginecólogo si sólo le atendió la matrona).

| ¿ESTÁ SATISFECHA CON … | Muy insatisfecha | Insatisfecha | Indiferente | Satisfecha | Muy satisfecha |
|---|---|---|---|---|---|
| **Factor I. Obstetra** | | | | | |
| La actitud del/de la ginecólogo/a en el parto (ej. respeto, amabilidad, escucha, etc.) | 1 | 2 | 3 | 4 | 5 |
| El interés y el trato personal que le prestó el/la ginecólogo/a en el parto | 1 | 2 | 3 | 4 | 5 |
| La información y explicaciones que le proporcionó el/la ginecólogo/a en el parto | 1 | 2 | 3 | 4 | 5 |
| La sensibilidad del/de la ginecólogo/a ante sus necesidades durante el parto | 1 | 2 | 3 | 4 | 5 |
| Los conocimientos, capacidad y competencia profesional del/de la ginecólogo/a durante el parto | 1 | 2 | 3 | 4 | 5 |

| | | | | | |
|---|---|---|---|---|---|
| La ayuda y el apoyo que recibió del/de la ginecólogo/a con las respiraciones y la relajación en el parto | 1 | 2 | 3 | 4 | 5 |
| Los cuidados físicos que recibió del/de la ginecólogo/a durante el parto (ej. movilidad, monitorización, tactos vaginales, etc.) | 1 | 2 | 3 | 4 | 5 |
| El tiempo que el/la ginecólogo/a pasó con usted durante la dilatación | 1 | 2 | 3 | 4 | 5 |
| La ayuda y el apoyo del/de la ginecólogo/a en el uso de distintos métodos para aliviar el dolor (ej. masajes, bolsa de agua caliente, ducha, inyección de agua, etc.) | 1 | 2 | 3 | 4 | 5 |
| **Factor II. Matrona** | | | | | |
| El interés y el trato personal que le prestó la matrona en el parto | 1 | 2 | 3 | 4 | 5 |
| La sensibilidad de la matrona ante sus necesidades durante el parto | 1 | 2 | 3 | 4 | 5 |
| La actitud de la matrona en el parto (ej. respeto, amabilidad, escucha, etc.) | 1 | 2 | 3 | 4 | 5 |
| La información y explicaciones que le proporciono la matrona en el parto | 1 | 2 | 3 | 4 | 5 |
| Los conocimientos, capacidad y competencia profesional de la matrona durante el parto | 1 | 2 | 3 | 4 | 5 |
| La ayuda y el apoyo que recibió de la matrona con las respiraciones y la relajación en el parto. | 1 | 2 | 3 | 4 | 5 |
| Los cuidados físicos que recibió de la matrona durante el parto (ej. movilidad, monitorización, tractos vaginales, etc.) | 1 | 2 | 3 | 4 | 5 |
| De forma global, la atención que usted recibió durante el parto | 1 | 2 | 3 | 4 | 5 |
| La ayuda y el apoyo de la matrona en el uso de distintos métodos para aliviar el dolor (ej. masajes, bolsa de agua caliente, ducha, inyección de agua, etc.) | 1 | 2 | 3 | 4 | 5 |
| El tiempo que la matrona pasó con usted durante la dilatación | 1 | 2 | 3 | 4 | 5 |
| De forma global, ¿cómo se siente de satisfecha con la experiencia del nacimiento de su bebe? | 1 | 2 | 3 | 4 | 5 |
| Su grado de participación en la toma de decisiones durante la dilatación | 1 | 2 | 3 | 4 | 5 |
| **Factor III. Dilatación** | | | | | |
| El control que tuvo sobre sus actos durante la dilatación. (ej. capacidad para relajarse, aguantar el dolor, poder moverse, beber, etc.) | 1 | 2 | 3 | 4 | 5 |
| Su capacidad para sobrellevar las contracciones durante la dilatación | 1 | 2 | 3 | 4 | 5 |
| Su experiencia global de la dilatación | 1 | 2 | 3 | 4 | 5 |
| La capacidad para afrontar sus emociones durante la dilatación (ej. ansiedad, miedos, inseguridad, etc.) | 1 | 2 | 3 | 4 | 5 |
| **Factor IV. Expulsivo** | | | | | |
| Su experiencia global del expulsivo | 1 | 2 | 3 | 4 | 5 |
| El control que tuvo sobre sus actos durante el expulsivo (ej. capacidad de relajarse, aguantar el dolor, cambiar de postura, etc.) | 1 | 2 | 3 | 4 | 5 |

| | | | | | |
|---|---|---|---|---|---|
| Su grado de participación en la toma de decisiones durante el expulsivo | 1 | 2 | 3 | 4 | 5 |
| La capacidad para afrontar sus emociones durante el expulsivo (ej. ansiedad, miedo, inseguridad, etc.) | 1 | 2 | 3 | 4 | 5 |
| **Factor V. Recién nacido** | | | | | |
| El tiempo transcurrido hasta que usted cogió en brazos por primera vez a su bebé | 1 | 2 | 3 | 4 | 5 |
| El estado de salud de su bebe al nacer | 1 | 2 | 3 | 4 | 5 |
| El tiempo transcurrido hasta que usted alimento por primera vez a su bebé | 1 | 2 | 3 | 4 | 5 |
| **Factor VI. Acompañante y confort** | | | | | |
| La ayuda y el apoyo de su pareja o acompañamiento durante la dilatación | 1 | 2 | 3 | 4 | 5 |
| La ayuda y el apoyo de su pareja o acompañamiento durante el expulsivo | 1 | 2 | 3 | 4 | 5 |
| Su grado de confort durante la dilatación (ej. ambiente íntimo, libertad de movimientos, compañía de la persona elegida, almohadas, mecedora, etc.) | 1 | 2 | 3 | 4 | 5 |
| Su grado de confort durante su expulsivo (ej. ambiente íntimo, postura cómoda, compañía de la persona elegida, etc.) | 1 | 2 | 3 | 4 | 5 |

## Supplemental material 3: Patient information sheet and informed consent form (PIS/ICF)

# Patient information sheet and informed consent form (PIS/ICF)

| | |
|---|---|
| **STUDY TITLE** | Cook´s balloon versus dinoprostone for Labour Induction of term pregnancies with fetal GROWth restriction (COLIGROW study) |
| **STUDY CODE** | COLIGROW |
| **PROMOTER** | Dr. Ignacio Herraiz García |
| **PRINCIPAL INVESTIGATOR** | |
| **CENTRE** | |

## Introductiono

We are writing to inform you about a research study in which you are invited to participate. The study has been approved by a Drug Research Ethics Committee and by the Spanish Agency for Medicines and Health Products, in accordance with current legislation, Royal Decree 1090/2015 of December 4 and European Regulation 536/2014. of April 16, which regulates clinical trials with drugs and health products.

Our intention is that you receive correct and sufficient information so that you can decide whether or not you agree to participate in this study. To do this, read this information sheet carefully and we will clarify any doubts that may arise.

In addition, you can consult with the people you consider appropriate.

## Voluntary participation

We invite you to participate in the study because you are a pregnant woman with a fetus who has been diagnosed with fetal growth restriction and who has already reached at least 37 weeks of pregnancy. At this point known as “full term pregnancy”, it is reasonable to recommend delivery. This recommendation is because, for the growth-restricted fetus, the risks of continuing to wait more weeks for spontaneous delivery to occur outweigh those of being born in the next few days. Furthermore, it is preferable for delivery to occur vaginally (if there are no reasons that contraindicate it) due to the indisputable advantages it has over a cesarean section: better recovery for the mother, easier initiation of skin-to-skin contact and breastfeeding, and fewer risks for future pregnancies, among others. To do this, it is necessary to induce labour (that is, start the labour process artificially) and choose the most appropriate method to carry out this induction.

You should know that your participation in this study is voluntary and that you may decide NOT to participate. If you decide to participate, you can change your decision and withdraw consent at any time, without altering your relationship with your doctor or causing any harm to your health care.

## Objective of the study

To induce labor, it is generally necessary to prepare the cervix, since in the vast majority of cases there have not been enough contractions previously for this to occur and the cervix will be closed and hard.

Today, we do not know what is the best method to prepare the cervix for pregnancies in which there is fetal growth restriction. A pharmacological method is usually used (vaginal dinoprostone), which consists of the application of a vaginal device that releases prostaglandins, which are hormones that help start the birth process. It is a very effective method and considered the first choice. We

believe that the mechanical method (Cook's double balloon) constitutes an alternative to vaginal dinoprostone, and consists of placing a device through the vagina that has a small double inflatable balloon at its tip, so that one of the balloons is lodged above and another below the cervix, once they are inflated with serum. Cook's balloon is also a method to induce labour, but it tends to be somewhat slower than pharmacological methods since it generally causes fewer contractions than prostaglandins. In return, it is possible that fetuses with growth restriction can better tolerate this slower rate of contractions.

With this study we want to evaluate whether Cook's double balloon allows for more vaginal births than the usual method (vaginal dinoprostone), without compromising the future baby.

## Study description

Approximately 172 patients in 5 Spanish centers are expected to participate in this study.

If you decide to participate in this study and meet its selection criteria, you will be randomly assigned, using a computer program, to one of the following treatment groups to induce labour: Cook´s balloon or dinoprostone. Being “randomized” for inclusion in the study means that you are assigned to a group at random (such as heads or tails). You will have the same chances of entering one group or the other.

If you are part of the Cook balloon group, a catheter with two small balloons will be placed at the level of the cervix (one immediately above and one below) with the help of a speculum and left lodged there (sometimes fixing the free end of the catheter to the thigh using a tape) until one of the following situations occurs: contractions begin in sufficient number and intensity, maturation of the cervix is achieved, the device is spontaneously expelled or 12 hours from its placement are exceeded.

If you are part of the pharmacological method group with dinoprostone, a prostaglandin-releasing device, similar to a “mini-tampax”, will be placed vaginally, which will be removed when contractions begin or when a maximum of 24 hours have passed since its placement.

Once the cervix has matured, the remaining birth and puerperium process will be carried out according to the usual protocols of each center. Before discharge from the hospital, you will be asked to complete a brief satisfaction survey.

## Study activities

The duration of your participation in the study is estimated at about five days from the signing of this informed consent until the end of follow-up after post-partum hospital discharge. The duration of the treatment phase is 12 or 24 hours.

The study plans to make four visits, which you will have to attend. They can usually be carried out coinciding with the visits necessary to monitor the pregnancy and postpartum period:

Visit 1 (or pre-screening, day -7 to -1): your medical history will be reviewed and completed, your blood pressure will be measured, a fetal ultrasound examination and, if your obstetrician deems it necessary, a vaginal examination will be performed. With all this, it will be possible to confirm that you meet the criteria to participate in the study: the existence of intrauterine growth restriction and the recommendation to induce labour after reaching week 37. You will be informed of the possibility of participating in this study and, if you decide to participate in it after reading the information in this document and answering your questions, you must give your informed consent in writing before starting visit 2. Finally, the date for visit 2 will be scheduled.

Visit 2 (or treatment, day 1 to 3): it will coincide with the day of admission for labour induction. A new vaginal examination will be performed to check the characteristics of the cervix and confirm the need for cervical ripening. If you no longer meet the conditions for cervical ripening, you will not be able to participate in the study. If you continue to comply with them, you will be randomized to one of the study groups, randomly assigned to one of the two induction methods: Cook's balloon or dinoprostone. Next, the assigned maturation method will be placed. This will begin the intervention (treatment), which will last a maximum of 12 hours in the case of the Cook´s balloon or 24 hours in the case of dinoprostone, corresponding to the maturation period of the cervix necessary for the induction of labour.

Visit 3 (or monitoring of labour and delivery, day 3 ± 2): it begins once the maturation of the cervix is completed and corresponds to the monitoring of the labour and delivery process. It will be the conventional one established by the protocols of the local center, although data related to the care of delivery and the newborn will be collected for the study, such as the time of the active phase of labor, type of anesthesia, type of delivery, and the newborn outcomes.

Visita 4 (or hospital postpartum follow-up, day 5 ± 2): It will be carried out during the postpartum period until hospital discharge. You will be asked to fill out a satisfaction survey (it will take between 10 and 15 minutes to complete). The existence or not of any type of maternal or neonatal complication upon hospital discharge will also be evaluated.

The tests that will be performed are routine in patients like you, they are not research or experimental tests.

## Risks and discomforts arising from your participation in the study

The two methods of labour induction used in this study have been used in humans for more than 10 years. Both methods are supported by the main clinical guidelines to be used in cervical ripening to achieve labour induction. Furthermore, both methods have approval from health authorities for this indication.

When medical treatment is started, there is a risk of the appearance of previously described side effects or new ones. Do not hesitate to inform your doctor of any disorder or discomfort you notice throughout the study.

The side effects associated with both methods are available through free access through the technical sheets of the respective products. However, information about them is offered below, based on their technical sheets. In the case of the Cook´s balloon (treatment considered “alternative” in this study), they are classified as:

| **Very common side effects: ≥ 10%** |
|---|
| • Discomfort during (mainly) or after placement. Usually well tolerated, occasionally it may cause withdrawal<br>• Failed induction and need for caesarean section |
| **Common side effects: from > 1% to < 10%** |
| • Risk of premature labour and birth in subsequent pregnancies (this risk could be slightly increased compared to the general population of pregnant women)<br>• Device expulsion |
| **Rare side effects: from 0,1 % to < 1 %** |
| • Rupture of membranes during insertion or spontaneous rupture of membranes<br>• Placental bleeding/abruption<br>• Uterine rupture<br>• Device compression and fragmentation<br>• Laceration of the cervix |

The comparator method, dinoprostone, has side effects similar to those described for the Cook´s balloon, although the risk of not achieving delivery after 24 hours is slightly lower and the risks of tachysystole and uterine rupture are slightly higher. In addition, it can occasionally cause systemic side effects such as fever, vomiting and diarrhea, which are usually mild and are well controlled with analgesics and antiemetics. According to its technical information, the side effects associated with dinoprostone are classified as:

| **Common side effects: from > 1% to < 10%** |
|---|
| • The baby may become distressed and/or its heart rate could become faster or slower than normal<br>• Increased contractions of the womb which may or may not affect the baby and discoloured amniotic fluid |
| **Rare side effects: from 0,1 % to < 1 %** |
| • Headache<br>• Decrease in blood pressure<br>• The newborn baby has difficulty breathing immediately after birth<br>• The newborn baby has high blood levels of bilirubin, a breakdown product of red blood cells, which can cause yellowing of the skin and eyes.<br>• Itching<br>• Heavy vaginal bleeding following delivery<br>• The placenta detaches from the wall of the womb before the baby is delivered<br>• Overall newborn condition depressed immediately after birth<br>• Slow progress in the birth process<br>• Inflammation of the membranes that are lining the inside of the womb<br>• The mother's uterus does not shrink after delivery due to lack of normal uterine contractions<br>• Feeling of burning in the genital area<br>• Fever |

| **Efectos secundarios de frecuencia desconocida en base a los datos disponibles** |
| --- |
| • Disseminated intravascular coagulation<br>• Anaphylaxis<br>• Hypersensitivity reaction<br>• Abdominal pain<br>• Nausea<br>• Vomiting<br>• Diarrhea<br>• Swelling of the genital areaPulmonary and amniotic fluid embolism<br>• Uterine rupture<br>• Cases of fetal and neonatal death have been reported after the application of dinoprostone, especially after the occurrence of serious events such as uterine rupture. |

**Risks and discomforts of the tests carried out as a result of the study**

Taking blood pressure and performing a transabdominal ultrasound are non-invasive and generally harmless procedures. The blood pressure cuff may cause slight discomfort and momentary skin irritation. The supine position (lying “upwards”) during the ultrasound can cause a feeling of dizziness and “cold sweat” due to compression of the maternal veins that return blood to the heart. You may also have this feeling if you get up quickly from the stretcher. If this happens to you, you should notify the study staff so that they can change your position, which usually causes the symptoms to subside in a short time and the risk of falling is avoided.

Vaginal examinations usually cause mild and temporary local discomfort. If you suffer from vaginismus (involuntary contraction of the vagina that causes pain and difficulty during the examination), inform the study staff who are going to examine you so that they can take extra care.

Completing the satisfaction survey does not involve any type of risk, since it consists of responding to a written survey.

**Participant responsibilities**

Tell your doctor about any medications you are taking during the study. This includes over-the-counter medication, prescription medications, herbal medicines, alternative medications, and vitamins. This is very important. If you have unusual symptoms, tell your doctor or the facility staff.

By signing this consent, you agree to follow the doctor's instructions and make all visits related to the study.

## Possible beneficts

There are no guarantees that you will gain any benefit from participating in this study, it may be the case that you will not gain any health benefits from participating in this study. The information obtained from this study may or may not help you or other women with a pregnancy with fetal growth restriction.

## Alternative treatments

If you do not participate in this study, you will likely be recommended a cervical ripening method to induce labor. This method will be chosen based on the center's protocols and your personal characteristics, with the use of dinoprostone being the choice in most cases. Talk to your study doctor who will give you more information if you want about possible alternatives before you decide if you want to participate in this study.

## Personal data protection

The promoter undertakes to comply with Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights and Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27 of 2016 of Data Protection (GDPR). The processing, communication and transfer of personal data of all participants will comply with the provisions of these rules.

Both the Center and the Promoter are respectively responsible for the processing of your data and undertake to comply with the data protection regulations in force. The data will be collected in a research file under the responsibility of the institution and will be processed within the framework of your participation in this study.

The data collected for the study will be identified by a code, so that no information that may identify you is included; only your study doctor/collaborators will be able to relate said data to you and your medical history. Therefore, your identity will not be revealed to any other person except the health authorities, when required or in cases of medical emergency. The Research Ethics Committees, representatives of the Health Authority in matters of inspection and personnel authorized by the Promoter (study monitors, auditors), will only be able to access to verify personal data, clinical study procedures and compliance of the standards of good clinical practice (always maintaining the confidentiality of the information).

In accordance with the provisions of data protection legislation, you can exercise your rights of access, modification, opposition and cancellation of data, for which you must contact your study doctor. Now you can also limit the processing of data that is incorrect, request a copy or have the data that you have provided for the study transferred to a third party (portability). To exercise your rights, contact the principal investigator of the study. We remind you that, if you decide to withdraw your consent to participate in this study, no new data will be added to the database, but if data that has already been collected will be used, this data cannot be deleted, even if you stop participating in the trial to ensure the validity of the research and comply with legal duties and drug authorization requirements. You also have the right to contact the Data Protection Agency if you are not satisfied.

Encrypted data may be transmitted to third parties, including outside the EU, to service providers or scientific researchers who collaborate with us, but your data will be protected by safeguards such as contracts or other mechanisms by data protection authorities. If you want to know more about it, you can contact the principal investigator of the study. The encoded data will in no case contain information that can directly identify you, such as name and surname, initials, address, social security number, etc. In the event that this transfer occurs, it will be for the same purposes of the study described or for use in scientific publications, but always maintaining their confidentiality in accordance with current legislation.

The Researcher and the Promoter are obliged to retain their data collected for the study for at least 25 years after its completion. Subsequently, your personal information will only be retained by the health care center and by the promoter for other scientific research purposes if you have given your consent to do so, and if permitted by applicable law and ethical requirements.

## Expenses and financial compensation

The promoter of the study is responsible for managing its financing. To carry out the study, the promoter has signed a contract with the doctor of the study and the center where it will be carried out.

You will not have to pay for study-specific products or tests.

## Other relevant information

A description of this trial will be available on the website www.ClinicalTrial.gov, where no information that could identify you is included (at most a summary of the results will be included).

Any new information regarding the products used in the study that may affect your willingness to participate in the study, which is discovered during your participation, will be communicated to you by your doctor as soon as possible.

You should know that you may be excluded from the study if the study promoter or investigators deem it appropriate, either for safety reasons, due to any adverse event that occurs due to the study medication, or because they consider that you are not complying with established procedures. In any case, you will receive an adequate explanation of the reason that caused your withdrawal from the study.

By signing the attached consent form, you agree to comply with the study procedures outlined to you.

## Contact in case of doubts

If during your participation you have any questions or need more information, please contact Dr. ……., Department of ……., contact phone…….

# INFORMED CONSENT FORM

| | |
|---|---|
| **STUDY TITLE** | Cook´s balloon versus dinoprostone for Labour Induction of term pregnancies with fetal GROWth restriction (COLIGROW study) |
| **Protocol code and version** | COLIGROW, v1.1 May 18th, 2023 |

……..

*(Name and surname of the participant)*

☐ I have read and understood the information sheet about the study.

☐ I have been able to ask questions about the study.

☐ I have received enough information about the study.

☐ I have spoken with …….

*(Name and surname of the investigator)*

☐ I understand that my participation is voluntary.

☐ I understand that I can withdraw from the study:

- Whenever I want.
- Without having to give explanations.
- Without this affecting my medical care.

I will receive a signed and dated copy of this informed consent document.

I freely give my consent to participate in the study.

Participant´s signature
Date:_____/____/_____
(Name, signature and date in the patient's handwriting)

Investigator´s signature
Date:_____/____/___

When the IC is obtained in people with modified capacity to give their IC

Signature of the legal representative, family member or de facto related person
Date:_____/____/_____
(Name, signature and date in the patient's handwriting)

Investigator´s signature
Date:_____/____/

I wish to be informed of information derived from research that may be relevant to my health:

☐ YES

☐ NO

Participant´s signature
Date:_____/____/_____

Investigator´s signature
Date:_____/____/___

(Name, signature and date in the patient's handwriting)

I agree that the doctors responsible for this study may contact me in the future in case it is deemed appropriate to request my permission for the use of the data from this study for future research not defined at this time, but related to the study or analysis.

☐ YES

☐ NO

Participant´s signature
Date:_____/____/_____

Investigator´s signature
Date:_____/____/___

(Name, signature and date in the patient's handwriting)

# Participant Consent Sheet before witnesses /

# INFORMED CONSENT FORM

| | |
|---|---|
| **STUDY TITLE** | Cook´s balloon versus dinoprostone for Labour Induction of term pregnancies with fetal GROWth restriction (COLIGROW study) |
| **Protocol code and version** | COLIGROW, v1.1 May 18th, 2023 |

I, ……<< *name and surname of the witness* >>, as witnesss, I affirm that in my presence Ms/Mrs ……<< *name and surname of the witness* >>, has been informed and the information sheet about the study has been read, so that:

☐ She has been able to ask questions about the study.

☐ She has received enough information about the study.

☐ She has spoken with ……

*(Name and surname of the investigator)*

☐ She understand that her participation is voluntary.

☐ She understand that she can withdraw from the study::

- Whenever she wants.
- Without having to give explanations.
- Without this affecting her medical care.

I will receive a signed and dated copy of this informed consent document.

Witness signature
Date:_____/____/____

Investigator´s signature
Date:_____/____/___

(Name, signature and date in the witness handwriting)

The participant wishes to be informed of information derived from research that may be relevant to her health:

☐ YES

☐ NO

Witness signature
Date:_____/____/____

Investigator´s signature
Date:_____/____/___

(Name, signature and date in the witness handwriting)

The participant agrees that the doctors responsible for this study may contact her in the future in case it is deemed appropriate to request her permission for the use of the data from this study for future research not defined at this time, but related to the study or analysis.

☐ YES

☐ NO

Witness signature
Date:_____/____/____

Investigator´s signature
Date:_____/____/___

(Name, signature and date in the witness handwriting)

The study participant has indicated that he cannot read/write.

A study staff member has read the consent document, reviewed and discussed it with the participant, and has been given the opportunity to ask questions or discuss it with others.

The witness must be an impartial person, outside the study.